UKPDS 26: Sulphonylurea Failure in Non-insulin-dependent Diabetic Patients over Six Years

UK Prospective Diabetes Study (UKPDS) Group[1]

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Patients with Type 2 (non-insulin-dependent) diabetes mellitus (DM) on sulphonylurea therapy convert to insulin progressively as the sulphonylureas 'fail'. The rate of failure and the features of those who fail have been poorly described. To assess secondary failure rates of sulphonylureas, we report on the responses in 1305 patients with newly diagnosed Type 2 DM randomly allocated to therapy with either chlorpropamide or glibenclamide in the UK Prospective Diabetes Study (UKPDS). These patients were initially treated by diet for 3 months and had a fasting plasma glucose >6 mmol l^{-1}; mean age 53 (SD 9) years; BMI 26.8 (SD 5.0) kg m^{-2}; and median fasting plasma glucose 9.1 (7.6–12.5 quartiles) mmol l^{-1}. If their fasting plasma glucose subsequently rose above 15.0 mmol l^{-1}, or they developed hyperglycaemic symptoms, additional hypoglycaemic therapy was given: metformin, ultratard insulin, and soluble insulin as required. By 6 years, 44 % had required additional therapy. Of those randomized to glibenclamide, 48 % required additional therapy by 6 years, compared with 40 % of those allocated to chlorpropamide ($p < 0.01$). Sixty-one per cent, 39 %, and 23 %, respectively, of patients with fasting plasma glucose ≥10.0 mmol l^{-1}, ≥7.8 mmol l^{-1} to <10.0 mmol l^{-1} and <7.8 mmol l^{-1} at randomization required additional therapy ($p < 0.001$). In the initial 3 years, non-obese subjects (BMI <30 kg m^{-2}) were more likely to require additional therapy than obese patients (BMI ≥30 kg m^{-2}) (43 % vs 53 % at 6 years; $p < 0.001$). Modelled beta-cell function showed that those with lower function were more likely to fail ($p < 0.0001$). Thus sulphonylureas fail as a therapeutic agent at rates which are dependent both on the phenotype at presentation and perhaps on the agent used initially. Higher failure rates were found in those with higher glucose concentrations, those who were younger, those with lower beta-cell reserve and those randomized to glibenclamide compared with chlorpropamide.

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Introduction

We report here on 1305 patients initially randomized to receive glibenclamide or chlorpropamide as part of the UK Prospective Diabetes Study (UKPDS).[1] Newly diagnosed diabetic patients were recruited at 15 centres throughout the United Kingdom and, after initial screening for suitability, assigned to 3 months of diet therapy. Patients who had a fasting plasma glucose (fpg) of >6 mmol l^{-1} were randomly allocated to glibenclamide or chlorpropamide as part of the UKPDS protocol.

Sulphonylurea therapy in those with Type 2 (non-insulin-dependent) diabetes mellitus (DM) has tradition-

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ally been regarded as 'failing' when patients are transferred onto insulin therapy. Failure rates have previously been estimated between 1.4 % and 5.6 % per annum.[2] However, the assessment of failure rates in previous studies has often been problematic in that the transfer of patients onto insulin therapy has been based on a physician's estimate of when patients had 'failed', and this assessment has been subjective or variably defined. By contrast, the UKPDS has a carefully defined protocol for failure that states that 'patients are to be maintained on the maximum dose of sulphonylurea until their fasting plasma glucose has risen to >15 mmol l^{-1} or they have developed hyperglycaemic symptoms'. The use of a protocol-defined failure rate allows us to examine the longitudinal trends in Type 2 DM for this particular threshold.

Sulphonylurea failure should be regarded as being distinct from sulphonylurea inadequacy.[3] *Failure* is the term generally used when further intervention is clinically necessary: the plasma glucose is too high for safety or hyperglycaemia is causing symptoms. *Inadequacy* implies that in spite of sulphonylurea therapy sufficient hyperglycaemia is present that there is a risk of complications of diabetes: the fasting plasma glucose concentration for this has been estimated from epidemiological studies as 7.8 mmol l^{-1} for microvascular disease in Type 1 diabetes[4] and 6.0 mmol l^{-1} for macrovascular disease.[5,6] UKPDS trial data on efficacy of therapies in reducing fasting plasma glucose and HbA_{1c} have already been published.[7]

There are two distinct aspects of interest in sulphonylurea failure. One is the overall likelihood of any particular sulphonylurea keeping patients symptom-free or their glycaemic control below 15 mmol l^{-1}. The second matter of interest to physicians is the question of whether it is possible to identify patients who are more likely to fail with sulphonylurea therapy and whether it is possible to estimate average 'survival times' on sulphonylurea monotherapy. To this end, we have documented the characteristics of patients in terms of fasting plasma

Table 1. Characteristics of 1305 patients studied at randomization after 3 months diet therapy. There are no significant differences between the demographic data of patients allocated to different sulphonylureas

n	1305
% Male	58.6
% White Caucasian	82
% Afro-Caribbean	9
% Asian	9
Age (years)[a]	52.7 (8.9)
Fasting plasma glucose at randomization (mmol l^{-1})[b]	9.1 (7.6, 12.5)
Haemoglobin A_{1c} at randomization (%)[b]	7.2 (6.3, 8.5)
Weight at randomization (kg)[a]	75 (15)
BMI at randomization (kg m^{-2})[a]	26.8 (5.0)
Plasma insulin at randomization (mU l^{-1})[c]	11.8 (6.5, 21.3)
%β (by HOMA modelling[d]) at randomization[c]	35.0 (15.8, 77.8)
%S (by HOMA modelling[d]) at randomization[c]	58.2 (32.4, 104.4)

[a]Mean (SD).
[b]Median (iqr).
[c]Geometric mean (1SD interval).
[d]Homeostatic Model Assessment.

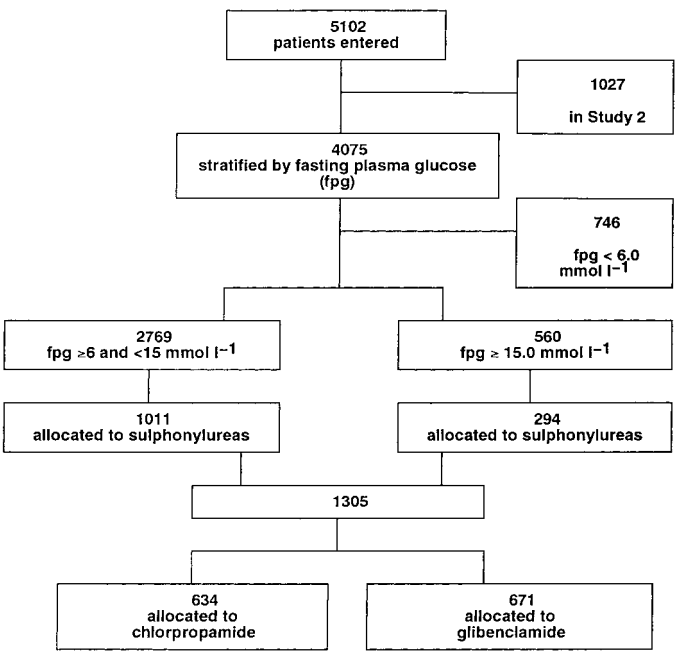

Figure 1. Randomization schedule of patients

glucose at diagnosis and randomization, body mass index, sex, and age at diagnosis. We have also calculated the index of beta-cell function by the Homeostatic Model Analysis (HOMA)[8] utilizing the fasting plasma glucose and insulin at randomization.

Methods

Patients Recruited

The UKPDS Study, which was begun in 1977, recruited 5102 patients aged between 25 and 65 years inclusive who were recently diagnosed as diabetic (two fasting plasma glucose estimations >6.0 mmol l^{-1}). Patients were excluded if they already had severe vascular disease, current angina, accelerated hypertension, proliferative or pre-proliferative retinopathy, renal failure (plasma creatinine >175 μmol l^{-1}) or life threatening disease (e.g. cancer). Also excluded were patients with severe asthma or another condition requiring systemic steroid therapy, those in an occupation that would preclude randomization to insulin therapy, those whose comprehension was insufficient to give informed consent to the trial, and those who presented with ketonuria >3 mmol l^{-1}. The trial had ethical approval and conforms to the Declarations of Helsinki 1975 and 1983.

Following recruitment, patients were seen monthly for 3 months and treated with a prudent diet containing approximately 50 % carbohydrate, low saturated fat and moderately high fibre. Obese patients were given a reduced energy content diet.[9] If, during these 3 months, patients failed to attend for clinic appointments they were not included for randomization. The randomization schedule of the patients is shown in Figure 1. Of the total patients recruited, 1027 were entered into a tight glycaemic-control protocol (Study 2). The remaining 4075 patients were stratified by their fasting plasma glucose; 746 were 'diet satisfactory' (fpg <6 mmol l^{-1}) and were not therefore randomized to sulphonylureas. Of the remaining 3329 patients (96 % had fpg ≥ 7.0

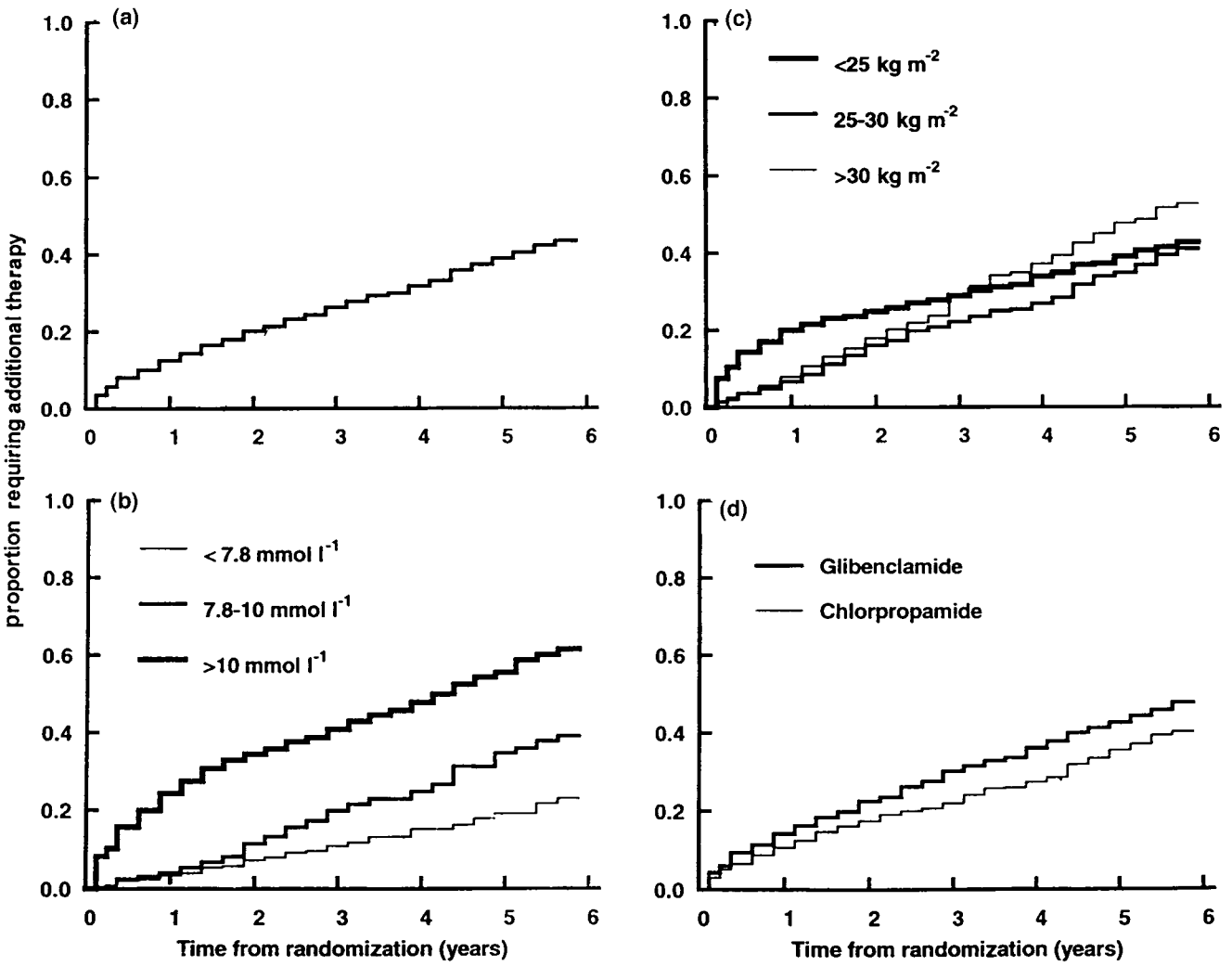

Figure 2. Kaplan–Meier estimates of proportion of patients requiring additional therapy. (a) All patients. (b) Patients sub-divided by fasting plasma glucose at randomization: ——— >10 mmol l ——— 7.8–10 mmol l ——— <7.8 mmol l. (c) Patients sub-divided by body-mass index: ——— <25 kg m^{-2} ——— 25–30 kg m^{-2} ——— >30 kg m^{-2}. (d) Patients allocated to ——— glibenclamide, and ——— chlorpropamide therapy

Table 2. Kaplan–Meier estimates of the proportion of patients requiring additional therapy at 6 years derived from those patients with data for all covariates

Classification variable	Level[a]	*n*	% Requiring additional therapy by 6 years	*p*-Value for long rank test
All		1246	44.1	
Therapy allocation	Chlorpropamide	604	39.9	
	Glibenclamide	642	47.5	0.010
Age	<54 years	623	49.5	
	≥54 years	623	38.7	<0.00001
BMI	<25 kg m^{-2}	518	42.7	
	25–30 kg m^{-2}	449	41.0	
	≥30 kg m^{-2}	279	52.7	0.057
Fasting plasma glucose	<7.8 mmol l^{-1}	359	23.0	
	7.8–10.0 mmol l^{-1}	354	38.9	
	≥10.0 mmol l^{-1}	533	61.2	<0.00001
%β	<27.1%	415	61.6	
	27.1%–55.1%	416	40.9	
	≥55.1%	415	27.9	<0.00001
%S	<44.4%	414	44.6	
	44.4%–71.5%	412	40.9	
	≥71.5%	418	46.1	0.11
HbA_{1c} (n = 1228)	<6.8%	389	26.4	
	6.8–8.6%	432	39.9	
	≥8.6%	407	56.0	<0.00001
Sex	Female	519	47.0	0.15
	Male	727	41.5	
Race	White Caucasian	1017	44.2	
	Afro-Caribbean	115	46.8	
	Asian	114	32.0	0.034

[a]Data are divided by quantiles or by clinically relevant values, where appropriate.

mmol l^{-1}), 1305 were randomized to sulphonylurea therapy and comprise the group considered by this paper.

Beta-cell function was assessed by Homeostatic Model Assessment (HOMA) analysis[8] and was undertaken on the 1246 patients who had insulin measurements at randomization.

The aim of therapy with sulphonylurea alone was to maintain the fasting plasma glucose below 6.0 mmol l^{-1} by increasing the dose to a maximum of 500 mg daily chlorpropamide or 20 mg daily glibenclamide. Thereafter patients were maintained on the maximum dose until their fasting plasma glucose rose to >15.0 mmol l^{-1} or they developed hyperglycaemic symptoms. At this point ('protocol-defined failure') additional therapy was introduced. For the purpose of the analysis in this paper, we have regarded the time at which additional therapy was introduced as being the moment of failure.

Following a protocol modification in 1988, 50 % of patients being treated with sulphonylurea alone and whose fasting plasma glucose was >6 mmol l^{-1} were randomly allocated to additional metformin and were considered censored from this time.

Clinic Visits and Biochemistry

At each 3-monthly visit clinical details were recorded (including hyper- or hypoglycaemic symptoms during the previous 3 months), together with a record of compliance with prescribed therapy and any symptoms or side-effects noted. A record of drug therapies, doses, and compliance was maintained. Blood samples were taken for biochemical analysis annually and full clinical examinations were carried out at 3-yearly intervals.

Plasma glucose assays were performed at each centre and monitored by the UKPDS Glucose Quality Assurance Scheme. Haemoglobin A_{1c} (HbA_{1c}) and insulin were analysed in the central laboratory. HbA_{1c} was measured by HPLC (Biorad Diamat, Biorad Ltd, Hemel Hempstead, Herts, UK), normal range 4.5–6.2 %, and insulin by radioimmunoassay (Pharmacia RIA100, Pharmacia Ltd, Milton Keynes, Bucks, UK), normal range 2.9–15.5 mu l^{-1}, with complete cross-reactivity to pro-insulin.

Data Handling and Statistics

Clinical data were double-punched for entry into a rule-based relational database system where range, trend, logical and combinatorial checks were performed.

Table 3. Cox proportional hazards model of factors predisposing towards 'failure' measured after 3 months' diet in patients with valid data for all covariates ($n = 1246$). Covariates are listed in order of inclusion in a stepwise model. Those below the line were not included in the model

	Risk factor	Risk ratio	95 % CI	*p*-Value
Fasting plasma glucose	<7.8 mmol l^{-1}	1.0		
	≥ 7.8 and <10.0 mmol l^{-1}	1.57	1.09, 2.27	0.015
	≥ 10.0 mmol 1^{-2}	2.49	1.65, 3.75	<0.00001
Age at diagnosis	≥ 54 years	1.0		
	<54 years	1.69	1.37, 2.09	<0.00001
β-cell function	≥ 55.1 %	1.0		
	≥ 27.1 % and <55.1 %	1.42	1.00, 2.02	0.052
	<27.1 %	2.38	1.53, 3.69	0.00011
Race	AS	1.0		
	AFC	1.30	0.76, 2.24	0.34
	WC	1.91	1.22, 3.01	0.0048
Sulphonylurea type	Chlorpropamide	1.0		
	Glibenclamide	1.45	1.181, 1.79	0.00043
Insulin sensitivity	≥ 75.1 %	1.0		
	≥ 44.4 % and <75.1 %	1.01	0.78, 1.31	0.94
	<44.4 %	1.18	0.86, 1.62	0.31
BMI	<25 kg m^{-2}	1.0		
	≥ 25 and <30 kg m^{-2}	0.85	0.66, 1.08	0.18
	≥ 30 kg m^{-2}	1.08	0.79, 1.46	0.63
Gender	Male	1.0		
	Female	1.08	0.87, 1.34	0.47

If haemoglobin A_{1c} is included in the model in place of fasting plasma glucose the order of inclusion becomes: haemoglobin A_{1c} > beta-cell function > age > sulphonylurea type > race, with BMI, insulin sensitivity, and gender still not being included.

Statistical analyses were performed using SAS® and BMDP® on the University of Oxford VAX Cluster. Data are expressed as mean (SD), or median (IQ range) or geometric mean (1 SD interval) as appropriate for the distributions of the data. Differences between distributions among groups were tested using non-parametric methods to avoid difficulties associated with non-normally distributed data.

Analysis of sulphonylurea failure was by allocation on an intention to treat basis. Kaplan–Meier survival analysis has been used in those patients who had all variables measured ($n = 1246$) to describe the failure rate associated with individual variables predisposing towards failure. A Cox proportional hazards regression model has been used to determine the relative risks for the different variables. Those patients who refused sulphonylurea therapy were included with those not requiring additional therapy, i.e. not failed, even though they were being treated with diet alone. These make up less than 4 % of the total allocated to sulphonylurea. Patients randomly allocated to added metformin in the later stages of the trial were considered censored at the visit of the random allocation. Those who did not complete the 6 years either because of death, loss to follow-up or not yet being in the trial for 6 years were considered censored at their last data acquisition visit.

Results

The demographic data are shown in Table 1. There were no significant differences between those allocated to chlorpropamide and those allocated to glibenclamide. More subjects were male than female, and the proportions randomized to either therapy reflect this. There were no statistical differences in allocation either by gender or by race.

The overall sulphonylurea failure rate shown by Kaplan–Meier survival curve is shown in Figure 2. By six years, 44 % of those randomized to sulphonylurea monotherapy had 'failed' and been transferred to other therapy (Figure 2(a)).

The survival curves for all patients as a function of the fasting plasma glucose at diagnosis are shown in Figure 2(b) (Table 2). The patients have been categorized into those whose fpg was <7.8 mmol l^{-1} (the WHO criteria for diagnosis of diabetes); between 7.8 and 10 mmol l^{-1}; and ≥ 10 mmol l^{-1}. The data show that the failure rate was significantly greater ($p = 0.00001$) in those who had fasting glucose ≥ 10 mmol l^{-1} at randomization, 61 % failing at 6 years. The patients who had fasting plasma glucose between 7.8 mmol l^{-1} and 10 mmol l^{-1} had a 6-year failure rate of 39 % and those

whose fasting plasma glucose at randomization was <7.8 mmol l^{-1}, had a 6-year failure rate of 23 % .

The Kaplan–Meier survival curves for all patients as a function of body mass index at randomization are shown in Figure 2(c) (Table 2). Patients have been allocated to groups with body mass index at randomization <25 kg m^{-2} (normal weight); ≥ 25 kg m^{-2} but <30 kg m^{-2} (defined as overweight); and ≥ 30 kg m^{-2} (defined as obese). Inspection of the curves shows that the normal weight group (<25 kg m^{-2}) had a greater failure rate during the first 2 years, but after this time became similar to the overweight group. The obese group were similar to the overweight group over the first 2 years, but thereafter had a greater failure rate. These survival fractions were not significantly different overall because of the non-proportionality of hazard over time.

The failure rate for patients allocated to chlorpropamide ($n = 604$) and glibenclamide ($n = 642$) are shown in Figure 2(d). There was a significant difference in failure rate between the two sulphonylureas. The 6-year failure rate for those allocated to glibenclamide was 48 % compared with the failure rate of those allocated to chlorpropamide of 40 % (log rank test for difference, $p = 0.011$). This is equivalent to delaying requirement for additional therapy by over a year for those on Chlorpropamide.

The data for other variables are shown in Table 2. Younger age, below the median 54 years, was significantly associated with failure ($p < 0.00001$). Beta-cell function assessed by HOMA[8] was inversely proportional to failure rates, 6-year rates being 28 %, 41 %, and 62 % for beta-cell function of >55 %, 27–55 % and <27 % respectively ($p < 0.00001$). No associations were found with insulin sensitivity (%S) in the HOMA model, gender or race. HbA_{1c} data reflected that demonstrated by fasting plasma glucose.

A Cox proportional hazards model was fitted to the data and the results are presented in Table 3. Fasting plasma glucose, age, beta-cell function and sulphonylurea type showed associations with $p < 0.001$. The risk ratio for plasma glucose >10 mmol l^{-1} compared with 7.8 mmol l^{-1} was 2.5; for age <54 years compared with those ≥ 54 years it was 1.7; for beta-cell function <27 % compared with those ≥ 55 % it was 2.4; and glibenclamide compared with chlorpropamide therapy was 1.5.

Discussion

'Sulphonylurea failure' needs to be defined before it can be quantified. This report uses the UKPDS definition of failure of an oral agent as a fasting plasma glucose rising above 15 mmol l^{-1} or symptoms attributable to hyperglycaemia (typically thirst or polyuria). Sulphonylurea inadequacy[3] is the issue of whether glycaemic levels can be maintained at a level to avoid complications. Past trials[10,11] suggest that this level could be set as a fasting plasma glucose >7.8 mmol l^{-1} for microvascular disease and 6.0 mmol l^{-1} for macrovascular disease. Glycaemic efficacy in the UKPDS has already been reported.[7]

The cause of sulphonylurea failure is generally accepted to be a declining function of the beta-cell rather than a failure of the drug itself.[12] This declining function is apparent in the data from all randomization options in the UKPDS, where glycaemic indices worsen with time regardless of whether the therapy was diet alone, insulin, metformin or sulphonylurea. The reasons for progressive loss of function of beta-cells in Type 2 diabetes remains obscure, but descriptions of amyloidosis in Type 2 DM offer one pathophysiological explanation.[13,14] Hyperglycaemia may itself have adverse effects (so called 'glucose toxicity'[15]) and glycation of proteins may exacerbate and hasten the demise of secretory capacity.

The data presented here show failure rates in patients recruited into the UKPDS study and remaining with a fasting glucose >6 mmol l^{-1} after 3 months diet. The overall failure rate was approximately linear, at about 7 % per annum. Those with a higher plasma glucose at randomization showed faster failure rates, and this is concordant with the hypothesis that such subjects have a lower beta-cell reserve and this is supported by the HOMA analysis. Thin patients fail faster than the more obese initially: thin patients are more likely to have anti ICA and anti GAD antibodies and have a Type 1 phenotype;[16,17] they have less leeway to alter their insulin sensitivity by weight loss; and some may have lost weight before diagnosis with relatively uncontrolled diabetes. A sub-set of data from the UKPDS has been previously analysed and reported and delineates the ICA and GAD antibody status and insulin requirements.[18] The results we report here may be skewed by ICA status, but we believe this is unlikely because of the small percentage effect of antibody status and the randomization of subjects. At the other end of the weight range those with sustained marked obesity also failed more rapidly, while optimal weight for non-failures was those having a body mass index between 25 and 30.

Clarke and Campbell[19] found no statistical difference between secondary failure rates of patients on glibenclamide or chlorpropamide, though the study was shorter (2 years duration) and smaller (321 patients) than ours. We have shown that patients treated with glibenclamide failed significantly faster than those given chlorpropamide with a relative risk of 1.5. Differences between the two sulphonylureas' actions may be responsible. Glibenclamide binds much more avidly to the sulphonylurea receptor than chlorpropamide and its therapeutic dose begins at 2.5 mg compared to that of 100 mg for chlorpropamide. Glibenclamide binds avidly to the beta-cell membrane near or at potassium efflux 'gates'. It is reasonable to suggest that constant block of the K+ATP channel may lead to an exhaustion of the beta-cell capacity to secrete insulin. It is possible that failing beta-cells have a life expectancy of secretion more a function of the amount of insulin they secrete than time-duration *per se*. Whether

chlorpropamide or glibenclamide influence morbidity or mortality will be apparent at the end of the study.

The Cox model (which is retrospective and not predictive) investigates some of the hierarchy of effects and suggests that failure can be described by functions of fasting plasma glucose at randomization, age at diagnosis, beta-cell function and sulphonylurea type.

In conclusion, sulphonylureas fail as a therapeutic agent at rates which are dependent both on the phenotype at presentation and on the agent used. Clarification of the mechanisms of failure may lead to an improvement in oral agents or clearer guidelines about their usage.

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